THE EFFECTS OF MODERATE DEFICIENCY OF VITAMINS*

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The physician in his practice has learned to recognize and to treat successfully the diseases due to the outspoken deficiency of vitamins. Those of us who live in the North know rickets; those in the Orient know beriberi; those in the South know pellagra; a few of the fortunate have seen xerophthalmia; and all are familiar with scurvy. We are told, however, that much ill-health is due to a moderate deficiency of vitamins; that the food of modern mankind, in the process of manufacture, selection and preparation, has lost some of its virtue. The laboratory worker, with his colonies of animals, discovers some half dozen new deficiencies a year; and suggests that symptoms in man, similar to those of his animals, are due to similar deficiencies. The manufacturer, given a little time, is able to furnish a preparation containing the indicated vitamin —succeeds in having clinical trials made, and finally so advertises the product to physician and often to layman, that the physician does not dare to neglect prescribing it for vague symptoms which puzzle him. Considerable money changes hands—some not infrequently finding its way into the research laboratory which holds the patent. But I would like to remind you that the real evaluation of each and every one of these remedies rests with the clinician. The physician Eijkman, in Java, noted that pigeons fed for economical reasons on boiled polished rice from the hospital kitchens, developed polyneuritis, resembling that of patients with beriberi. The Danish pediatrician, Bloch, showed that xerophthalmia and night blindness could be cured by cod liver oil, but not by sunlight; also that these conditions occurred independently of rickets;

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thus clearly proving that the disease is not akin to rickets, and furnishing evidence of the existence in cod liver oil of two vitamins. The clinical experiments of Dr. Alfred Hess have established the value of vitamin C in the prevention and cure of infantile scurvy; and have greatly clarified the problem of the nature and action of vitamin D in rickets. I would further remind you that a coöperation is proper and necessary between the reputable manufacturer and the clinician in the study of the wider, more vague, field of moderate vitamin deficiencies.

The physician who undertakes to prove that any morbid condition is due to a lack of a specific vitamin, must establish four criteria: (1) The condition in question must disappear wholly or in part when the vitamin is administered. This, however, may not occur, if irreparable damage has been done; if the vitamin is not absorbed, as may happen, with fat-soluble vitamins in steatorrhea; and if other deficiencies are not corrected. For example, diets deficient in vitamin D are often also deficient in calcium and phosphorus. Very often also, a morbid condition may be due to several factors. The development of infectious diseases depends upon exposure; virulence of the infecting organism; resistance of the host. Diet in such cases cannot be expected to afford complete protection; only a careful statistical analysis can afford any proof of the existence of a significant deficiency of a vitamin. (2) Administration of the vitamin must prevent wholly or in part the development of the morbid condition. (3) The beneficial effect, if any, ascribed to the vitamin must be proved not to be due to some other action of the preparation—certain preparations of vitamin B contain sugars, whose caloric value cannot be ignored in producing a gain in weight. Highly purified vitamins—for example A, C and D; possibly B_1—are now available for use in crucial experiments. This question is not merely academic. The proof of a definite deficiency will make possible the proper selection of a dietary of natural foodstuffs. It will counteract the recent tendency to administer to babies mixtures which resemble the fast disappearing shot-gun prescription. (4)

The existence of mild or latent deficiency may be studied by the use of refined methods of measurement. Tests of visual acuity might reveal latent deficiency of vitamin A; the test for capillary fragility of Göthlin may be a measure of deficiency of vitamin C; the X-ray may reveal unsuspected evidence of rickets. Such tests must be interpreted with all due caution. When a research worker discovers by X-ray a form of rickets which does not yield to appropriate treatment, the burden of proving that the condition is rickets still rests with him.

Certain forms of evidence are presumptive; in themselves insufficient, but highly suggestive. The non-existence in his environment of frank cases of beriberi, pellagra, rickets, scurvy or night blindness, is taken as evidence against the existence in the patient of a corresponding latent deficiency. Due regard must then be paid to the special conditions prevailing in the patient—such as illness, early age, rapid growth, pregnancy, which might create an increased need for vitamins. Requirements of an animal species for vitamins cannot be applied uncritically to man, but often have been. The increase of intake of a vitamin far beyond the usual quantity may not relieve a condition, such as the tendency to repeated infection. This cannot be used as an argument that the condition in question may not be aggravated if the intake of vitamin is lowered. Chemical analyses of tissues for vitamins are at present beginning to supplement biological tests. These analyses must be accepted with the greatest reserve; and cannot obviate the necessity for actual clinical trial of a carefully planned diet. They may be of great value in conjunction with delicate tests for the actual presence of disease due to the deficiency.

We may now turn to a consideration of some of the more definite evidence of latent dietary deficiency. In spite of the marked decline in death-rate from diarrhea and certain specific contagious diseases, the mortality in the first days of life and the high incidence of prematurity and of still-birth continue. Evidence that faulty diet during

pregnancy may be in large part responsible for this mortality is accumulating. Toverud, working is Oslo, has found that the Norwegian diet especially in winter, results in a negative balance of calcium and of phosphorus; that this can easily be prevented by the use of more milk, green vegetables, fruit, and cod liver oil. The birth-weight of full-term infants was thereby increased; and the percentage of premature births among unmarried mothers dropped from 32 per cent (in the obstetrical clinic) to 2 per cent among the mothers cared for by Toverud. At the Maternity Center of New York by careful supervision of hygiene during pregnancy, the incidence of premature births has been reduced to 1/3 of that prevailing in the general population of the City. Several factors of course play a role in the decrease of the rate of premature birth. The dietary deficiency undoubtedly includes that of calcium, phosphorus and vitamin D.

The typical disease due to lack of vitamin D is rickets. Other factors may play an etiologic role—such as the diet of the mother during pregnancy; low birth weight; and rapid growth. The effect ascribed by E. Mellanby to cereals in the production of rickets may in part be due to rapid growth or to the low assimilation of the phosphorus in cereal. The phosphorus of cereals is present chiefly as inositol hexaphosphate; which is not only poorly absorbed but which also precipitates calcium, and thus prevents its absorption. In certain cases of rickets, the typical symptoms and signs, although present, may not be so prominent as signs usually regarded as minor: for example, extreme irritability. We have observed several cases in which the irritability disappeared within a few days, while the serum phosphate rose in response to ultraviolet radiation. In another case, sweating was profuse; the hands were red and swollen, and the skin of the fingers was macerated and infected—suggesting acrodynia. However, the blood pressure was normal and signs of rickets were obvious; the abnormal condition of the hands rapidly disappeared under antirachitic treatment. Such cases may have given rise to the idea that ultraviolet therapy is bene-

ficial in acrodynia. We have not found it so. Another condition allied to rickets, but with none of the skeletal changes is the tetany occurring in children of low birth weight within the first six weeks of life. Such cases usually respond in a dramatic manner to intensive antirachitic therapy. Dental caries in older children has been ascribed by M. Mellanby to dietary deficiency, particularly to a relative deficiency of vitamin D and to a diet high in cereals. Boyd and his coworkers report that dental caries may be arrested by a diet containing pigmented vegetables, fresh fruit, butter, milk and cod liver oil. Hanke and his coworkers believe that the addition of one pint of orange juice and the juice of one lemon to the ordinary diet will check the development of caries. Disagreement prevails among competent workers in regard to the relative effect of diet and of acid-producing microorganisms in causing caries. More carefully controlled clinical studies are now in progress in several places; and we should soon know more definitely which are the important factors.

Definite indications exist that a relative deficiency of vitamin C may exist in certain parts of the world, even where scurvy is rare. Göthlin and his colleagues have refined a test for capillary fragility—first proposed by Dr. Hess; by aid of this, it has been possible to show in two adults that the capillaries of the skin become more fragile after a diet low in vitamin C had been taken for several weeks; and returned to normal within a few weeks after a diet high in vitamin C had been resumed. A rather extensive survey among school children in northern Sweden revealed the presence of a considerable number in whom the capillary fragility was increased. A good correlation existed between this and the low antiscorbutic value of their diets. Gingivitis appeared more frequently in the children with increased fragility, but was present also in the others. Gerstenberger has used fresh fruit in large quantities in the treatment of aphthous and ulcerative stomatitis, apparently with success. Hanke and his coworkers have made extensive studies in which one pint per day of orange juice

appears to have greatly decreased the incidence and severity of gingivitis in a community of children at Mooseheart. They imply that the effect is due to vitamin C. It must, however, be pointed out that owing to its carotene content, orange juice may have a vitamin A activity greater than that of milk. It also contains an appreciable amount of calcium. The anemia in scurvy may yield to orange juice. Rohmer and Bindschedeler describe prescorbutic anemia in infancy—accompanied by poor growth in weight and stature, irritability, anorexia, and puffiness of the face, feet and hands. In several of their cases, cure of the anemia could not be accomplished with a dried cabbage juice rich in vitamin C, until iron also was added.

Deficiency of the vitamin B complex has long been suspected in the dietary of infants, largely on the basis of assays using experimental animals. Maurer, reasoning on rather a priori grounds, believes that neonatal death is due to insufficient vitamin B in the diet of the mothers during pregnancy. The importance of this subject would justify a most extensive study. Hoobler, Bloxsom, Dennett and others have described a symptom-complex in children 6-12 months of age, which they ascribe to relative deficiency of vitamin B. The symptoms are anorexia, pallor, loss of weight or stationary weight, irritability, and muscular rigidity. The symptoms yield to the use of yeast, yeast extracts, and preparations of wheat germ. The effect, however, may be due in large measure to a greater intake of food. From our own experience, we can say that many cases with similar symptoms do not respond to this treatment. We have felt that the chief etiological factors in our cases were faulty methods of feeding, or the presence of infection. In the latter type, we have often observed immediate and lasting improvement following the use of 1 or 2 units of insulin twice a day continued for a week or ten days. Vitamin B may be relatively deficient in the diet of older children. In an admirably planned clinical experiment, Summerfeldt of Toronto, shows that the expected average gain in weight in a group of children can be

increased four times over a period of three weeks by the use of a special cereal, in place of ordinary cereal. These gains were maintained. It is difficult to know whether such gains are really optimal; whether they may reasonably be attributed to vitamin B is also open to some question, because the cereal furnished also considerable additional minerals, including calcium, phosphorus and iron. Patients with chronic diarrhea may be given diets low in vitamins; they may also absorb vitamins poorly. It seems likely that the smoothness of the tongue noted in some of these conditions may be caused by partial lack of vitamin B_2; for it is relieved by giving brewer's yeast.

Vitamin A has been the subject of recent clinical study by Dr. Hess and his colleagues. There can be no doubt from their investigations that the administration of large quantities of vitamin A in the form of haliver oil, or provitamin in the form of carotene, did not confer the slightest additional power upon infants to resist respiratory infections. This is to be attributed to the fact that these children were already receiving a diet rich in vitamin A. According to Sutliff and Segool, cod liver oil will not prevent otitis media as a complication of scarlet fever. We have found that carotene is also ineffective (Figure 1). On the other hand, it seems possible from a study of the carotinoid content of the blood, which we have carried out, that about 15 per cent of children over the age of two years, may avoid foods rich in carotene, and as a consequence about 1/3 of them may be subject to repeated respiratory infection. We feel also that a diet rich in vitamin A may be desirable in the first few months of life. It is known that infants—especially of low birth weight—may have in their tissues a comparatively very low store of this vitamin. Although they may not at this time be subject to infection, owing to the presence of protective substances acquired from the mother, they may later on show increased susceptibility, unless they receive more vitamin A than is present in milk alone. We have carefully studied two groups of infants in the out-patient department.

The Effect of Oral Administration of Carotene During Scarlet Fever

Cases Uncomplicated at Onset			Cases Complicated at Onset			
No Carotene 21 Cases	Carotene 13 Cases		No Carotene 13 Cases		Carotene 16 Cases	
		Complications	Initial	After 1 wk.	Initial	After 1 wk.
1	0	Otitis	8	1	8	8
2 (same case)	0	Mastoiditis	0	5	1	13
1	2	Adenitis	2	4	3	2
0	1	Arthritis	0	1	0	0
0	0	Sinusitis	2	0	3	1
0	0	Abscess	1	0	2	3
0	0	Empyema	1	0	0	0
0	0	Peritonitis	0	2	0	0
2	3	Other	0	2	0	2
0	0	Died	—	1	—	1
4.3	5.2	Av. Stay, Wks.	6.9		6.1	

Fig. 1.

Infections of Infants as Affected by Diet

From Barenberg and Lewis, New York City and Maxwell, Rochester, N. Y.

	New York City		Rochester, N. Y.	
	C. L. O.	Viosterol	Good	Bad
J. F. M.	0.35	0.25	0.24	0.50
A. M. J.	.23	.18	.15	.22
J. A. S.	.19	.15	.08	.14
O. N. D.	.33	.17	.23	.32

Fig. 2.

Eighty of these received cod liver oil at least from the age of two months; most of them from the age of two weeks; and until at least the age of six months. From this time, they received pigmented vegetables. The rate of infection (number of infections per infant per month) is nearly the same as that in the series of Barenberg and Lewis (Figure 2). The other group of 40 infants received no cod liver oil; until after the age of four months. Many of them received vegetables from the age of six months. The milder

respiratory infections—rhinitis, pharyngitis, otitis media —occurred with equal frequency in both groups, excepting in the early Spring months (Figure 3). In the various

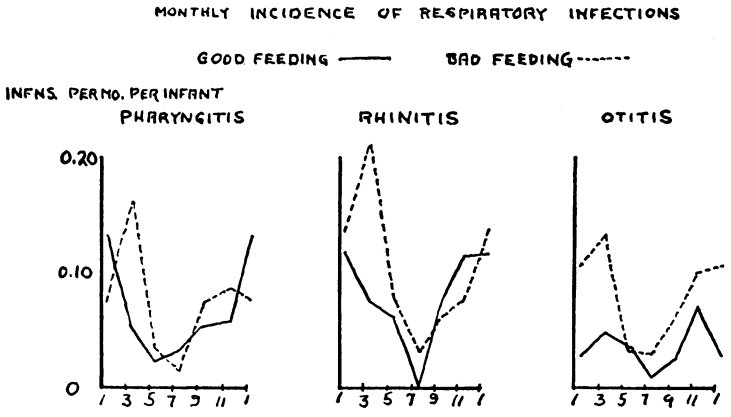

Fig. 3.

age groups, there is little difference in the incidence of rhinitis and pharyngitis, but a marked increase in the incidence of otitis media in the poorly-fed group after the age of six months (Figure 4). We feel that our groups are too small to permit very certain conclusions, and we would emphasize the difficulty in excluding other causes than

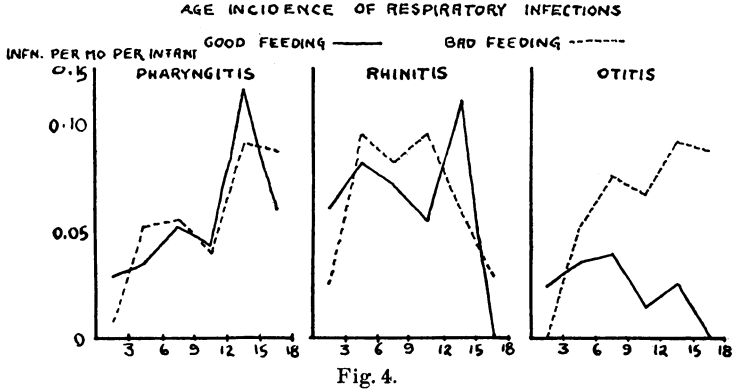

Fig. 4.

faulty diet. In another study, we have some evidence that early feeding of cod liver oil may prevent the occurrence for severe infections, such as pneumonia, mastoiditis, and septicemia (Figure 5). Here we are dealing with only a

Correlation of Infections with Previous Feeding

DIET		0-6 Mos.					6-24 Mos.				
			INFECTIONS, %					INFECTIONS, %			
C. L. O.	Veg.	Number	O	Mod.	Sev.	Sev. Total	Number	O	Mod.	Sev.	Sev/Total
0	0	35	40	37	23	0.38	50	14	40	16	0.54
+	0	27	56	29	15	0.34	21	9.5	86	4.5	0.05
0	+						77	25	60	15	0.21
+	+						56	41.1	55.4	3.5	0.06

DIET		2-6 Yrs.					6-14 Yrs.				
			INFECTIONS, %					INFECTIONS, %			
C. L. O.	Veg.	Number	O	Mod.	Sev.	Sev. Total	Number	O	Mod.	Sev.	Sev/Total
0	+	267	32.5	55.1	12.4	0.18	712	55.9	39.6	4.48	0.10
+	+	124	60.5	34.7	4.8	0.12	123	62.6	32.5	4.88	0.13

Fig. 5.

single observation in each case, and relying upon the history as well as we could obtain it. In another study we have analysed the records of about 700 children who entered the hospital before the age of three years. We have considered separately the sexes; have indicated the ratio of severe to non-severe infections; and have attempted to correlate the influence of (a) bad diet as causing severity of infection; and (b) exposure to children of school age in the family as causing severity of infection. These two latter correlations are based upon Yule's method of coefficients of contingency. A coefficient of plus one is regarded as a perfect correlation; plus 0.5 as very good; zero, as absence of relation. Good diet is defined as before—cod liver oil from the age of two months to at least six months; either cod liver oil or vegetables from the age of six months. The age-incidence (Figure 6) of relatively severe

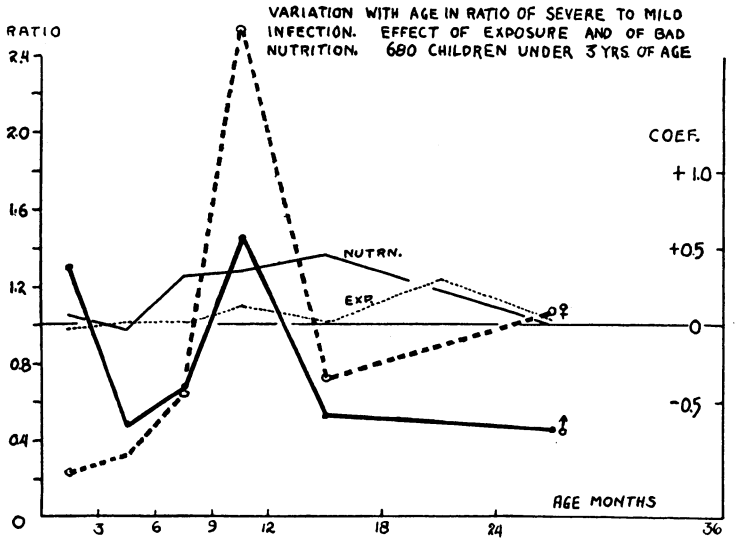
VARIATION WITH AGE IN RATIO OF SEVERE TO MILD INFECTION. EFFECT OF EXPOSURE AND OF BAD NUTRITION. 680 CHILDREN UNDER 3 YRS OF AGE
RATIO
2.4
2.0
1.6
1.2
0.8
0.4
0
COEF.
+1.0
+0.5
0
-0.5
NUTRN.
EXP.
3
6
9
12
18
24
30
AGE MONTHS

Fig. 6.

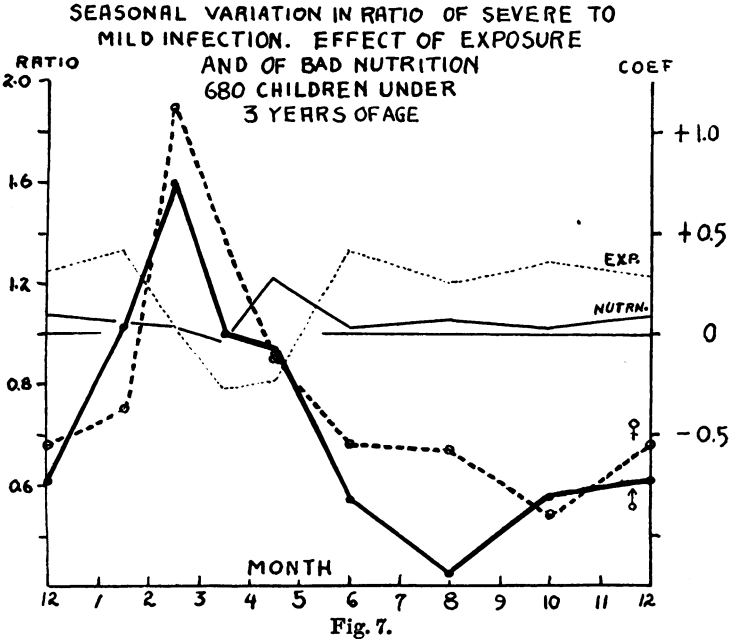
SEASONAL VARIATION IN RATIO OF SEVERE TO MILD INFECTION. EFFECT OF EXPOSURE AND OF BAD NUTRITION 680 CHILDREN UNDER 3 YEARS OF AGE
RATIO
2.0
1.6
1.2
0.8
0.6
COEF
+1.0
+0.5
0
-0.5
EXP.
NUTRN.
MONTH
12
1
2
3
4
5
6
7
8
9
10
11
12

Fig. 7.

infection indicates that boys are relatively much more liable than girls under the age of three months. Thereafter, girls are more liable. This is regarded as an effect of constitution. Exposure to older children—and incidentally—greater economic distress—cannot account for the high incidence in both sexes of relatively severe infection between the ages of nine and twelve months. On the other hand, there is some evidence that the relative severity of infection may be associated with poor diet consumed in the earlier months of life. In the seasonal incidence of severe infections (Figure 7), we observe that the sexes are affected nearly alike; the girls suffering somewhat more at all times. Infants who have a severe infection during the summer months are likely to have had previously a poor diet. The very marked increase in severity of infection in February is not related to exposure, and only to a slight degree related to faulty diet in the earlier months. We may regard this high peak of severe infections as due either to more massive exposure, or to increased virulence of the infection. These studies are not offered with a view of settling the question of the relationship of vitamin A to infection; but rather, in order to keep the question open. They indicate, moreover, that the factors involved in infection are many, including constitution (sex, even during infancy), exposure, the nature of the infection, and probably also diet. I would stress in particular that if vitamin A has any anti-infective power, it should be administered in the earliest months when the growing organism may need larger quantities, and when a deficiency is more likely to exist.